12, lines 33-35, at page 18, lines 22-30 and page 59, lines 18-36 through page 60, line 9 of the specification. Additionally, support for claims 30-34 directed to transgenic mice exhibiting a hypoactive phenotype and having a disruption in a melanocyte stimulating hormone receptor gene, methods of producing said transgenic mice and cells and tissues isolated from said mice may be found, for example, at page 18, lines 22-24, page 19, lines 33-35, page 21, lines 11-22, page 39, lines 28-29 and page 59, lines 18-36 through page 60, line 9 of the specification. Lastly, support for claim 35 directed to transformed cells may be found, for example, at page 2, lines 29-35 of the specification. As such, no new matter has been added.

Amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in related applications. Moreover, the amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation or continuation-in-part application.

Upon entry of the amendments, claims 26-35 are pending in the instant application.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

A. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH.

Claim 8 was rejected under 35 U.S.C. § 112, first paragraph for allegedly being non-enabling to one skilled in the art to make the invention commensurate with the scope of the claim. Applicants respectfully traverse this rejection. However, in view of the cancellation of Claim 8, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, is moot.

Claims 17-20 have been rejected for allegedly failing to provide enablement for a heterozygous knockout mouse or a melanocyte stimulating hormone receptor gene-disrupted mouse. The Office Action provides that the above-mentioned claims, "while being enabling for a homozygous melanocyte stimulating hormone receptor gene knockout mouse, . . . [do] not reasonably provide enablement for a heterozygous melanocyte stimulating hormone receptor [gene] knockout mouse." Applicants respectfully traverse this rejection. However, in view of the cancellation of Claims 17-23, the Examiner's rejection under 35 U.S.C. § 112, first paragraph,

is moot.

Applicants submit that new claims 26-35 are fully enabled by the teachings of the specification. As the rejection under 35 U.S.C. § 112, first paragraph of claims 8 and 17-20 is no longer relevant as a result of the cancellation of these claims, and new claims 26-35 are fully enabled by the teachings of the specification, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

B. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH.

Claims 1-4, 9-10 and 21 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, claims 1-4 and 10 were rejected under 35 U.S.C. § 112, second paragraph, on the assertion that the arrangement of the targeting construct is unclear. Claims 9 and 21 were rejected under 35 U.S.C. § 112, second paragraph, on the assertion that the word "derived" renders the claim indefinite because the nature and number of derivative processes is unknown. Also, claim 21 was asserted to be indefinite because it refers to the "transgenic mouse of claim 20" however, claim 20 is drawn to a method of producing a transgenic mouse.

Applicants respectfully traverse each rejection under 35 U.S.C. § 112, second paragraph. However, in light of the cancellation of claims 1-10 and 17-21, these rejections under 35 U.S.C. § 112, second paragraph, are moot. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Applicants submit that new claims 26-35 are definite and particularly point out and distinctly claim the subject matter regarded as the invention in accordance with 35 U.S.C. § 112, second paragraph.

C. REJECTION UNDER 35 U.S.C. § 102(E).

1. Cone et al.

Claims 1-10 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Cone et al (U.S. Pat. No. 6,278,038).

To anticipate a claim, a reference must teach every element of the claim. "A claim is anticipated [under §102] only if each and every element as set forth in the claim is found . . . in a single prior art reference." MPEP §2131 *citing* (Verdegaal Bros. V. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)).

It has been asserted by the Office Action that Cone describes the practice of generating melanocyte stimulating hormone receptor knockout mice via homologous recombination. The newly added claims describe homozygous knockout mice that exhibit hypoactivity. Nowhere does Cone discuss a hypoactive phenotype of the knockout mice. As such, Cone fails to disclose a targeting construct containing a DNA sequence homologous to a melanocyte stimulating hormone receptor gene or methods of producing such a construct wherein mice homozygous for the disruption exhibit hypoactivity. Accordingly, Cone does not teach every element of the claimed invention.

Because Cone fails to teach homozygous melanocyte stimulating hormone receptor knockout mice, which exhibit hypoactivity, Cone fails to anticipate the claimed invention. As such, the rejection of Claims 1-10 under 35 U.S.C. § 102(e) as being anticipated by Cone et al (U.S. Pat. No. 6,040,138) may be withdrawn.

D. REJECTION UNDER 35 U.S.C. § 103(A).

Claims 1-8 and 10 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Mansour et al. (1998) *Nature* 336(24):348-352 in view of Mountjoy et al. (1992) *Science* 257:1248-1251 and Adachi et. al. (1999) *J. Immunology* 163:3363-3368.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP §2143.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

New claims 26-35 are non-obvious over the teachings of the prior art references. More particularly, the claimed invention relates to the *in vivo* mammalian characterization of the function of the melanocyte stimulating hormone receptor gene, and provides transgenic animals and cells comprising disruptions in melanocyte stimulating hormone receptor genes and methods and compositions relating thereto, which are not obvious in view of the teachings and disclosures of the references cited by the Examiner.

According to the Office Action, Mansour describes a targeted disruption of the *hprt* and proto-oncogene *int-2* in mice embryonic stem cells, and subsequent generation of knockout mice. The Office Action asserts that the disclosure of Mansour relates to a general method for isolating embryonic stem cells containing a targeted mutation in an endogenous gene. More particularly, it was asserted that Mansour describes the targeted disruption of the *hprt* gene and the proto-oncogene *int-2* in mouse embryonic stem cells by homologous recombination using targeting constructs specific for these genes. Applicants submit that Mansour does not teach or suggest a targeting construct containing a DNA sequence homologous to a melanocyte stimulating hormone receptor gene or methods of producing such a construct as recited in the newly added claims. Applicants also submit that Mansour fails to describe a method of producing a transgenic mouse comprising a homozygous disruption in a melanocyte stimulating hormone receptor gene as claimed by the present invention.

Mountjoy et. al., as characterized by the Office Action, describes the cloning of a mouse melanocyte stimulating hormone receptor gene. Accordingly, the nucleotide sequence of a mouse melanocyte stimulating hormone receptor is provided. The reference is not concerned with a targeting construct containing a DNA sequence homologous to a melanocyte stimulating hormone receptor gene or methods of producing such a construct as recited in the newly added claims. Applicants submit that Mountjoy does not teach or suggest a targeting construct containing a DNA sequence homologous to a melanocyte stimulating hormone receptor gene or methods of producing such a construct as recited in the newly added claims. Applicants also submit that Mountjoy fails to describe a method of producing a transgenic mouse comprising a homozygous disruption in a melanocyte stimulating hormone receptor gene as claimed by the present invention. As such, Mountjoy et. al. is absent of any teaching or suggestion of disrupting

the melanocyte stimulating hormone receptor gene, and in particular, to produce the transgenic mice, targeting constructs, tissues, cells, and methods as recited in the pending claims. Thus, Mountjoy *et al.* fails to make up the deficiencies in Mansour and as such, the presently claimed invention is not obvious.

Adachi et. al., as characterized by the Office Action, describes that a melanocyte stimulating hormone receptor may be expressed on a stimulated mast cell line and that the hormone inhibits the release of histamine from mast cells. The Office Action also asserts that Adachi describes that a melanocyte stimulating hormone receptor may be involved in cell proliferation and cytokine production in inflammatory tissue. Applicants submit that Adachi does not teach or suggest a targeting construct containing a DNA sequence homologous to a melanocyte stimulating hormone receptor gene or methods of producing such a construct as recited in the newly added claims. Applicants also submit that Adachi fails to describe a method of producing a transgenic mouse comprising a homozygous disruption in a melanocyte stimulating hormone receptor gene as claimed by the present invention. As such, Adachi et. al. is absent of any teaching or suggestion of disrupting the melanocyte stimulating hormone receptor gene, and in particular, to produce the transgenic mice, targeting constructs, tissues, cells, and methods as recited in the pending claims. Thus, Adachi *et al.* fails to make up the deficiencies in Mansour and as such, the presently claimed invention is not obvious.

In view of the cited references, one of ordinary skill in the art would not have been motivated to provide a produce the transgenic mice, targeting constructs, tissues, cells, and methods as recited in the pending claims. Accordingly, new claims 26-35, as amended, are not obvious under 35 U.S.C. § 103(a) over Mansour in view of Mountjoy et. al. and further in view of Adachi *et al.*, and, as such, this rejection may be withdrawn.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

Respectfully Submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

September 26, 2002

Claims 1-10 and 17-21 have been cancelled.
Claims 11-16 and 22-25 have been withdrawn from consideration.

We claim:

26. (New) A targeting construct comprising:

(a) a first polynucleotide sequence homologous to a first portion of a melanocyte stimulating hormone receptor gene;

(b) a second polynucleotide sequence homologous to second portion of a melanocyte stimulating hormone receptor gene; and

(c) a selectable marker located between the first polynucleotide sequence and the second polynucleotide sequence,

wherein the targeting construct when introduced into murine embryonic stem cells, results in a transgenic mouse having a disruption in a melanocyte stimulating hormone receptor gene, wherein the mouse when homozygous for a disruption in a melanocyte stimulating hormone receptor gene exhibits hypoactivity.

27. (New) The targeting construct of claim 26, wherein the targeting construct further comprises a screening marker, the screening marker positioned outside either the first polynucleotide sequence or the second polynucleotide sequence and opposite the selectable marker.

28. (New) A method of producing a targeting construct for a melanocyte stimulating hormone receptor gene, the method comprising:

(a) obtaining a first polynucleotide sequence homologous to a first region of a target gene;

(e) obtaining a second polynucleotide sequence homologous to a second region of a target gene;

(f) providing a vector comprising a selectable marker; and

(g) inserting the first and second sequences into the vector to produce the targeting construct,

wherein the targeting construct when introduced into murine embryonic stem cells, results in a transgenic mouse having a disruption in a melanocyte stimulating hormone receptor gene, wherein the mouse when homozygous for a disruption in a melanocyte stimulating hormone receptor gene exhibits hypoactivity.

29. (New) A method of producing a targeting construct for a melanocyte stimulating hormone receptor gene, the method comprising:

(a) providing a polynucleotide sequence homologous to a target gene;

(b) generating two different fragments of the polynucleotide sequence;

(c) providing a vector having a gene encoding a selectable marker; and

(e) inserting the two different fragments into the vector to form the targeting construct, wherein the targeting construct when introduced into murine embryonic stem cells results in a transgenic mouse having a disruption in a melanocyte stimulating hormone receptor gene, wherein the mouse when homozygous for a disruption in a melanocyte stimulating hormone receptor gene exhibits hypoactivity.

30. (New) A method of producing a transgenic mouse comprising a homozygous disruption in a melanocyte stimulating hormone receptor gene, the method comprising:

(a) introducing a melanocyte stimulating hormone receptor gene targeting construct into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(e) breeding the chimeric mouse to produce the transgenic mouse comprising a homozygous disruption in a melanocyte stimulating hormone receptor gene, wherein the mouse when homozygous for a disruption in a melanocyte stimulating hormone receptor gene exhibits hypoactivity.

31. (New) A method of producing a transgenic mouse comprising a homozygous disruption in a melanocyte stimulating hormone receptor gene, the method comprising:

(a) providing a mouse embryonic stem cell comprising a disrupted melanocyte stimulating hormone receptor gene; and

(b) introducing the mouse embryonic stem cell into a pseudopregnant mouse, wherein the pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse, wherein the mouse when homozygous for a disruption in a melanocyte stimulating hormone receptor gene exhibits hypoactivity.

32. (New) A transgenic mouse comprising a homozygous disruption in a melanocyte stimulating hormone receptor gene, wherein the transgenic mouse exhibits hypoactivity.

33. (New) A cell or tissue isolated from the transgenic mouse of claim 32.

34. (New) A transgenic mouse comprising a heterozygous disruption in a melanocyte stimulating hormone receptor gene, wherein said disruption in a homozygous state inhibits production of a functional melanocyte stimulating hormone receptor gene protein resulting in a transgenic mouse exhibiting hypoactivity.

35. (New) A cell transformed with the targeting construct of claim 26, wherein the cell comprises a disruption in a melanocyte stimulating hormone receptor gene.